Lasers in Surgery and Medicine 21:42–49 (1997)

Importance of Using Rigorous Statistical Methods to Analyze Low Energy Laser Experimental Data: Part Two

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Background and Objective: **Numerous authors have reported successful alteration of peripheral nerve action potential characteristics through application of low energy laser irradiation (LELI). The statistical analysis that accompanies many of these reports frequently does not account for the special nature of the data generated in typical LELI experiments. The objective of this study was to evaluate the application of repeated measures linear regression techniques to the analysis of this type of data. Issues of analyzing raw versus normalized data, proper accounting for correlation between measurements, and discrete time point hypothesis testing were addressed.**

Study Design/Materials and Methods: **The data analyzed in this work were generated from an experiment in which in vitro frog sciatic nerves were irradiated with a helium-neon laser using a variety of treatment protocols. Compound action potential (CAP) amplitude, latency, depolarization rate, and repolarization rate were recorded at 1-minute intervals for 135 minutes for each nerve. Laser-induced changes in CAP parameters were analyzed using various repeated measures linear regression models.**

Results: **The findings of statistical significance were highly dependent on the rigor of the regression model applied. Application of the same regression model to raw and normalized data produced different findings of significance. Determination of significant contrasts was highly dependent on how well the regression model accounted for the correlation between repeated measurements made on the same nerve. In general, models that failed to account adequately for this correlation produced more findings of significant contrasts than increasingly rigorous models. Finally, discrete time point hypothesis testing on normalized data can suggest improper statistical conclusions if the proper correlation structure is not applied to the data set.**

Conclusion: **Linear regression analysis offers advantages over discrete time point hypothesis testing in the analysis of highly correlated serial data of this type. Trends in the behavior of the measured parameters are evident, rigorous accounting for correlation between measurements is facilitated, and hypothesis testing is highly flexible. Lasers Surg. Med. 21:42–49, 1997**

Key words: biostimulation; HeNe laser; low intensity laser therapy; repeated measures linear regression analysis; statistical methods

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Accepted 23 September 1996.

INTRODUCTION

Use of low energy laser irradiation (LELI) to enhance wound healing, pain relief, and nerve repair and regeneration has been a subject of interest for more than 15 years [see 1–5 for reviews]. Reports of LELI-induced alteration of healthy and injured peripheral nerve function [6–12] offer tremendous potential to generate efficacious clinical treatments of peripheral nerve injuries and disease if the reported laser-induced effects can be replicated and verified.

In a companion work [13], we reported the results of an experiment in which in vitro frog sciatic nerve compound action potential (CAP) characteristics were measured under a range of LELI conditions. The data set generated in the course of that work was typical of those found in other studies of the effect of LELI on peripheral nerve tissue characteristics in vitro and in vivo. Since the study of the effect of laser irradiation on the function of peripheral nerve tissue often requires the collection of repeated electrophysiological measurements made on the same nerve preparation over time, many LELI studies make use of serial measurements taken at discrete time points preirradiation, during irradiation, and postirradiation.

Experiments that measure changes in CAP parameters in response to irradiation over minutes, hours, or days frequently rely on statistical comparisons made at discrete time points to demonstrate the effect of the laser irradiation on the tissue. Due to the inherent variability of biological data, CAP behavior at any arbitrary time point may or may not be indicative of the overall laser-induced trend of that CAP parameter during that phase of the experiment. If the CAP parameters at the chosen time points happen to be greatly different than the behavior of the parameter at other times during that phase of the experiment, the statistical conclusions drawn may be incorrect and misleading. Furthermore, important statistical dependencies of successive measurements are often ignored in discrete time point methods. Another disadvantage to the use of discrete time points to describe LELI effects is that trends in laser-induced alterations of CAP parameters are lost, although this information is necessary to understand completely the influence of LELI on the tissue.

In the companion work [13], repeated measures linear regression analysis was introduced to examine the data for evidence of laser-induced changes in the CAP. This statistical method is well suited to the analysis of repeated measurements taken on the same tissue over a defined time period, a commonly encountered type of data set in investigations of laser effects in peripheral nerve tissue. Although this form of regression analysis has not been previously applied in LELI research of this sort, it was found to offer significant advantages over discrete time point statistical methods encountered in the LELI literature.

In particular, the use of regression modeling in this experiment proved valuable as a means of capturing the trends in behavior of the measured CAP parameters over the various phases of the experiment. Additionally, this method of analysis permitted rigorous accounting for the strong correlation between the repeated measurements. Hypothesis testing was also enhanced by use of regression analysis since discrete time points could be compared while capturing the trend in the CAP behavior over time and properly accounting for the strong correlation noted between measurements made on the same nerve.

The purpose of the current work was to explore fully the utility of using repeated measures linear regression analysis to analyze peripheral nerve electrophysiological data collected serially in the course of an LELI experimental protocol. Following a general explanation of the application of repeated measures linear regression analysis in this context, some important ramifications of using linear regression analysis are further investigated. Among these ramifications are differences in the statistical conclusions obtained when using raw measurements of CAP parameters versus normalized measurements, the effect of rigorously accounting for the strong serial correlation between measurements on the same nerve preparation, and the potential advantages of using regression analysis over discrete time point hypothesis testing in data sets of this type.

MATERIALS AND METHODS

A full description of the materials and methods is provided in the companion work [13] and is not repeated here. Following is a brief overview of the experimental methods employed.

Tissue Preparation, Irradiation, and CAP Recording

The sciatic nerves in each leg of large bullfrogs were harvested and laid over five wire electrodes in separate nerve chambers. Following a

60-minute baseline CAP recording period, 15 minutes of HeNe laser (632 nm, Spectra Physics Model 125) irradiation was delivered to the surface of one of the two nerves via a 0.6 mm diameter optical fiber at the site in which the nerve contacted either the ground electrode or proximal recording electrode. Laser output power was varied among the treatment groups that were designated according to the combination of mean total energy delivered to the tissue and site of irradiation (see table in companion work). The contralateral nerve in the nonirradiated chamber was assigned to the control group.

Throughout the experiment, each nerve was stimulated at 1-minute intervals using a supramaximal stimulus (0.025 ms, 1.5 V). The resulting CAP was recorded differentially via a MacLab stimulator-A/D converter unit and saved on a computer for off-line measurement of CAP amplitude, latency, rate of depolarization, and rate of repolarization. CAP amplitude was measured from peak to peak; latency was measured from stimulus onset to the negative peak of the CAP. The rates of depolarization and repolarization of the evoked CAP were estimated by measuring the slope of the CAP trace on either side of the negative peak.

CAP recording in each nerve was performed in three consecutive phases that totaled 135 minutes. In phase 1, which required 60 minutes, baseline characteristics of each nerve were established by stimulating and recording evoked CAPs once per minute. Phase 2 consisted of 15 minutes of irradiation delivered to the nerves assigned to irradiated treatment groups. During phase 2, CAPs were simultaneously evoked and recorded in irradiated and nonirradiated nerves at 1-minute intervals. In phase 3, the postirradiation phase, CAPs were stimulated and recorded at 1-minute intervals in both nerves for an additional 60 minutes.

Statistical Analysis

a. Optimum linear regression model for normalized data. Normalized measurements were computed by determining the mean value of each CAP parameter over the 60-minute preirradiation recording period for each nerve. All subsequent raw CAP parameter measurements recorded in that nerve were divided by the mean preirradiation value of the appropriate parameter to derive the normalized value of the CAP parameter corresponding to that time point in the given nerve.

By graphically examining individual response profiles in each treatment group, it was determined that the optimum way to analyze the data was by separate linear regression models for each of the three experimental phases: preirradiation (Phase 1), irradiation (Phase 2), and postirradiation (Phase 3). A random-coefficient linear regression analysis for unbalanced repeated measures was performed on the normalized CAP parameters for each phase-treatment group combination using the SAS computer program. Akaike Information Index (AII) and Swartz-Bayesian Criteria (SBC) goodness-of-fit indices were used to determine the relative success of each linear regression model in fitting the data [14,15]. Larger AII and SBC indices were indicative of regression models that fit the data more closely.

The data strongly suggested that measurements in the same phase recorded nearer in time were more highly correlated than measurements taken farther apart in time (e.g., normalized amplitude data yielded a correlation coefficient > 0.91). To account for this strong serial correlation between measurements made on the same nerve in the same phase of a treatment group, a first-order autoregressive covariance structure was included in the regression model. The autoregressive covariance structure, which is commonly applied in repeated measures regression analysis, models the correlation between two measurements as a function of the time lapse between the measurements [14]. In this work, it was assumed that the correlation between measurements made on a nerve within the same phase decreased exponentially as the time between measurements increased.

The random-coefficient aspect of the linear regression model provided a second competing mechanism to account for correlation between serial measurements. In this scheme, the measurement correlation was also assumed to be a function of the time lapse between measurements, although the exact form of this function was not exponential, but depended on the degree of heterogeneity of the regression slopes fit to individual nerves in the treatment group. The function resulted in a maximum correlation when measurements were taken very close to one another and rapidly dropped off as the time between measurements increased.

The covariance structure of the response was taken as the sum of the covariance of each of the components, the autoregressive structure, and the random coefficient portion of the model. AII

and SBC goodness of fit indices confirmed that simultaneous inclusion of these two methods of correlation modeling optimized the fit of the regression model relative to other correlation structures attempted.

Hypothesis testing was conducted on contrasts that measured differences in regression line slope between two phases in a treatment group relative to the difference in slopes in the control group between the same two phases: e.g., is the change in regression line slope between phase 1 and phase 3 in Group 1 G different than the change in slope between phase 1 and phase 3 in the nonirradiated control group? By arranging contrasts in this manner, comparisons of laser-induced trends in CAP parameters in a given phase with trends demonstrated in the control group were possible, simultaneously accounting for nonlaser-induced changes in regression line slope due to confounding factors (e.g., decreasing nerve viability over time). The overall threshold for significance ($\alpha = 0.05$) was adjusted by the Bonferroni method to reflect multiple comparisons [16].

A special shorthand notation was developed to describe concisely the various contrasts tested. Each label included the CAP parameter measured, the treatment group, the site of irradiation, and the two phases being compared. For example, the contrast "latency, 4 R Phase 3:1" denotes that the difference in regression line slope between phase 3 and phase 1 in treatment group 4 R was compared to the same difference in the nonirradiated control group for CAP latency.

b. Analysis of normalized versus raw data. One commonly encountered data analysis technique found in many LELI studies is normalization of CAP measurements to some preirradiation value, although frequently this preirradiation value is not explicitly specified. In this section, the same repeated measures linear regression model was fit to both normalized and raw CAP measurements to determine if different statistical conclusions would be generated.

Initial attempts to use the optimum random coefficient regression model previously fit to the normalized data failed when attempting to fit the raw data due to the occasional inability of the computer program to converge to unique values of the regression equation coefficients. A likely explanation for this program convergence failure is that in some cases the two competing methods of correlation accounting were so similar numerically that it was difficult to determine how much weight each method was responsible for in the correlation structure. In these instances, the similarity between the autoregressive structure and the random coefficient regression was so large that a "ridge" was created in the maximum likelihood estimate. On this ridge of possible regression equation coefficients, several choices were approximately equally appropriate and the program was incapable of converging to a true maximum.

Therefore, the regression model that was fit to the raw and normalized CAP measurements was slightly reduced in scope from the optimum model described previously. The reduced regression model differed from the optimum model in that only the autoregressive covariance structure was utilized to account for the correlation between measurements. Of the competing mechanisms of correlation accounting, elimination of the random coefficient aspect of the model provided the best fit to the raw CAP measurements. All other aspects of the model and hypothesis testing were the same as described previously. According to the AII and SBC goodness of fit indicators, the reduced regression model fit the normalized data only slightly less closely than the optimum model (e.g., for CAP amplitude, $AII_{full} = 5{,}928$, $AII_{reduced} = 5{,}894$; $SBC_{full} = 5{,}915$, $SBC_{reduced} = 5{,}885$).

c. Effect of correlation accounting. Repeated measurements on single nerves are frequently encountered in LELI-peripheral nerve interaction investigations, as it is important to follow irradiation-induced alterations in tissue function over time. Serial measurements of this type tend to be highly correlated and not independent, necessitating special consideration during statistical analysis. In order to determine the impact of properly accounting for the correlation between serial measurements, a series of five regression models were fit to the normalized data. Each successive regression model contained less rigorous accounting for the correlation present between measurements.

The first model chosen (Model 1) was the optimum regression model for the normalized data discussed previously. Correlation between measurements was accounted for by the combination of the autoregressive covariance structure as well as the random coefficient nature of the regression model. Model 2 corresponded to a regression model in which the only the autoregressive covariance structure was used to model the measurement correlation. In Model 3, a random coefficient

regression model was fit to the normalized data, but no autoregressive covariance structure was included. Model 4 was constructed so that the correlation between measurements made in any phase was assumed to be uniform and not vary as a function of the time lapse between measurements. The final model, Model 5, assumed that all CAP measurements were independent of each other and demonstrated no correlation. Hypothesis testing proceeded as previously described.

d. Discrete time point hypothesis testing vs. regression analysis. In order to compare directly the statistical conclusions derived from regression analysis to discrete time point statistical methods, paired Student *t*-tests were used to compare irradiated group mean values to control group mean values at each time point (i.e., once per minute over the 135-minute experiment) at a significance level of $\alpha = 0.05$. Statistical conclusions derived based on these *t*-tests were compared to conclusions derived from regression line slope contrasts determined from application of the optimum regression model to normalized data.

Student *t*-tests were also conducted between irradiated and control values at the midpoint in each phase using the fitted regression lines derived from the optimum model applied to normalized data. For these tests, the overall significance level of $\alpha = 0.05$ was adjusted by the Bonferroni method to reflect multiple comparisons. The findings of significance generated by these *t*-tests were compared to those computed from directly testing the normalized CAP measurements prior to fitting the regression models.

RESULTS

a. Optimum Linear Regression Model for Normalized Data

The effect of HeNe laser irradiation on CAP parameters as determined by the optimum regression model fit to normalized data is fully discussed in the companion work [13]. Briefly, laser irradiation under the experimental conditions described failed to induce any statistically significant change in CAP amplitude, rate of depolarization, and rate of repolarization at any time in the experiment. Only one contrast, 7 R Phase 3:1 (i.e., treatment group 7 R, postirradiation phase) demonstrated a statistically significant increase in latency compared to the nonirradiated control group over the same time period.

b. Analysis of Normalized vs. Raw Data

The reduced regression model fit to the raw CAP measurements resulted in one finding of significance, namely, that treatment group 7 R demonstrated increased latency in the postirradiation phase relative to the nonirradiated control group (7 R Phase 3:1, $P = 0.0003$).

Fitting the same regression model to the normalized data also resulted in the finding that treatment group 7 R demonstrated significantly increased latency relative to the control group (7 R Phase 3:1, $P = 0.0001$). One additional finding of significance was noted, however. Treatment group 4 R latency was determined to be greater than the nonirradiated control group latency in the postirradiation phase (4 R Phase 3:1, $P = 0.0191$). Furthermore, a contrast that narrowly missed achieving the required level of significance in the raw data (latency, 4 R Phase 2:1, $P = 0.026$) was far from achieving significance when analyzed as normalized data ($P = 0.1551$).

c. Effect of Correlation Accounting

In order to determine the effect of correlation accounting on the findings of significance, five progressively less rigorous regression models were fit to normalized CAP data. The results of this experiment are shown in Table 1. The number of findings of significance was greatest in the model that assumed uniform correlation between measurements and did not take into account the fact that measurements taken closer together in time were most highly correlated.

d. Discrete Time Point Hypothesis Testing vs. Regression Analysis

As previously indicated, the only contrast determined to be significant under the optimum regression model applied to normalized data was CAP latency, 7 R Phase 3:1. Student *t*-tests conducted on normalized CAP measurements prior to fitting a regression model resulted in findings of significant differences in latency treatment group 7 R at 35–37, 39–51, 53, and 55–60 minutes postirradiation. However, Student *t*-tests conducted on the fitted regression lines at the midpoint of each phase demonstrated no significant differences in any treatment group.

DISCUSSION

Analysis of Normalized vs. Raw Data

The regression model that produced the optimum fit to the normalized data, as determined

TABLE 1. Results of Correlation Accounting Experiments*

Model	Model assumptions	Significant contrasts	CAP parameter	*P* value
1	Random coefficients Autoregressive cov.	7 R Phase 3:1	Latency	0.0158
2	Autoregressive cov.	4 R Phase 3:1	Latency	0.0191
		7 R Phase 3:1	Latency	0.0001
3	Random coefficients	None	—	—
4	Uniform correlation	1 G Phase 2:1	Latency	0.003
		1 G Phase 3:1	Latency	0.0004
		4 R Phase 2:1	Latency	0.0055
		4 R Phase 3:1	Depolar. rate	0.0001
		7 R Phase 3:1	Latency	0.0001
		4 R Phase 3:1	Depolar. rate	0.0001
5	No correlation	4 R Phase 3:1	Latency	0.0001
		7 R Phase 3:1	Latency	0.0001
		4 R Phase 3:1	Depolar. rate	0.0001

*In each treatment group (1G, 4G, 4R, and 7R), four contrasts were tested for each of the four CAP parameters measured. Therefore, a total of 16 contrasts were tested in each treatment group. Only those contrasts that achieved statistical significance under the five regression models tested are listed.

by the goodness-of-fit indices, suggested that only one contrast achieved the required level of significance, the 7 R Phase 3:1 contrast applied to CAP latency. When the same model was fit to the raw data, however, difficulties with program convergence forced a modification to reduce the extent of the correlation accounting. This reduced regression model, when applied to the raw CAP measurements, confirmed the results of the optimum model by finding only the CAP latency contrast 7 R Phase 3:1 to be statistically significant.

Application of the reduced regression model to the normalized data, however, produced slightly different results. Although the reduced model applied to normalized data confirmed the significance of the latency contrast 7 R Phase 3:1, a second contrast (latency, 4 R Phase 3:1) was also determined to have achieved significance. Furthermore, a contrast that narrowly missed achieving the required level of significance under the raw data (latency, 4 R Phase 2:1) was determined to be quite far from significance under the normalized data.

The fact that use of raw and normalized data produces different statistical conclusions should not be surprising. In each case, the parameters measured are on different scales. Consequently, one can reject the equality of regression line slopes on one scale and fail to reject equality on the other scale. It is possible to construct artificial data sets in which it can be mathematically proven that equality of slopes on one scale in different phases of the experiment does not guarantee equality of slopes on another, normalized scale.

In the case of complex data sets such as those resulting from most LELI studies, it is not possible to develop a general rule to predict differences in the statistical conclusions expected using normalized data versus using raw data. It is more likely that the phenomenon of producing different answers depending on which type of data is used is dependent on the actual structure of each individual data set. In situations in which laser-induced differences are very clear between irradiated and nonirradiated treatment groups, both raw and normalized data are likely to provide the same answers, at least qualitatively. Unfortunately, many LELI studies report subtle differences in laser-induced parameters that are, therefore, subject to the type of data set chosen for analysis.

Effect of Correlation Accounting

The investigation of the effects of correlation accounting in the application of repeated measures linear regression analysis to normalized CAP data produced interesting and unexpected results. In general, it was expected that the use of less rigorous models would fail to capture the correlated nature of the data and, therefore, lead to more findings of significance. One method of conceptualizing correlation accounting is by noting that the effective sample size decreases as more rigorous accounting is made for the measurement correlation. Smaller effective sample sizes usually lead to fewer findings of significance, but more honestly represent the way the experiment was actually conducted. In contrast, regression models that use a covariance structure that is not as rig-

orous, such as Model 4, effectively utilize a sample size on the order of the number of measurements made, rather than the number of nerves contained in the treatment group. Using an inflated sample size in this manner typically renders findings of statistical significance more likely.

Interestingly, use of Model 4, which assumed uniform correlation between measurements, led to multiple findings of significance, suggesting that the laser irradiation was relatively effective in altering the measured CAP characteristics. When a more rigorous model such as Model 1 is fit to the same data, a completely different conclusion is evident regarding the efficacy of the laser irradiation in this tissue. Previous studies that report wide-ranging success with using LELI to alter the characteristics of peripheral nerve tissue must be carefully evaluated, especially with regard to the statistical methods utilized to confirm those claims. It is possible that in many cases, claims of significant laser-induced findings may be due to improper application of statistical methods, as demonstrated by use of Model 4 on this data set.

It is not as straightforward to compare Models 2 and 3, which both included similar methods of accounting for correlation. In this data set, inclusion of the autoregressive covariance structure produced findings similar to the optimum model. The model that utilized the random coefficient method of correlation accounting, however, found no contrasts to be significant. This points out the importance of proper and thorough correlation accounting when analyzing serial data of this type. As the goodness-of-fit indicators demonstrated, the correlation of the data was best accounted for by inclusion of both methods of correlation accounting.

Discrete Time Point Hypothesis Testing vs. Regression Analysis

Many LELI studies of laser-peripheral nerve interaction generate serial data by making repeated measurements on the same tissue and analyzing the results via hypothesis testing at discrete time points. In this work, comparisons were made between Student *t*-tests performed on the normalized data and the findings of significance from both the regression line slopes and *t*-tests conducted at discrete time points using fitted values of the optimum regression equations. Student *t*-tests conducted on discrete time points resulted in the general finding of significant differences in latency in treatment group 7 R during the postbaseline period. Testing of regression line slopes demonstrated similar conclusions. However, discrete time point testing of regression model fitted values revealed no contrasts of significance in any treatment group.

The reason that the discrete time point testing following regression differs so dramatically from testing prior to regression modeling involves issues discussed previously. Specifically, *t*-tests conducted directly on the normalized data in no way account for the strong correlation structure present in the measurements. The same tests, conducted after fitting the best possible model to the data, rigorously accounted for this correlation and thus found no significant differences at discrete time points. Failure to analyze this data set properly by use of a rigorous regression model would have led to erroneous reports of statistically significant laser-induced changes in the measured CAP characteristics.

One other point is also important to note about discrete time point hypothesis testing. In studies in which laser irradiation is applied to peripheral nerve tissue over time, it is often important to track trends in the behavior of the electrophysiological properties of interest. Use of regression analysis enables trends in this behavior to be captured without the loss of information that occurs when using discrete time point hypothesis testing. If discrete time point testing is desired for some reason, the fitted values of the regression equation should be utilized for this purpose.

CONCLUSIONS

The results of this work confirmed that repeated measures linear regression analysis provides additional insight into understanding the action of low energy laser irradiation on peripheral nerve tissue. In particular, use of regression analysis enables full retention of the information captured in all phases of the experiment, since it does not rely on an arbitrary choice of a limited number of discrete time points as the basis of comparison. Rather, the trend in the behavior of the treatment group over a given time period is clearly evident and easily quantified.

Linear regression modeling, as applied in this work, was also found to provide a flexible hypothesis testing scheme. From measurements collected in this study, it was possible to test multiple contrasts simultaneously, once the appropriate regression model had been fitted. Traditional use of discrete time point hypothesis testing is

inevitably limited to comparisons of irradiated means to control means or postirradiation versus preirradiation comparisons made within a treatment group. The flexibility in hypothesis testing and contrast generation offered by regression analysis can provide information and statistical conclusions not readily available from tests conducted only at discrete points. If testing of specific contrasts at discrete time points is desired, however, regression analysis offers the ability to accomplish this, at the same time, properly accounting for the correlation structure of the measurements.

One of the frequently ignored aspects of LELI-peripheral nerve interaction studies is correlation induced in measurements when multiple CAP recordings are made on the same tissue preparation over time. In an experiment in which the CAP is measured repeatedly from the same nerve at certain time intervals, it is expected that CAP measurements recorded closer in time depend more strongly on one another and thus are more highly correlated than measurements made further apart in time. The strong correlation pattern holds true for measurements made over minutes, hours, or days. Discrete time point hypothesis testing techniques often neglect the repeated nature of the measurements and fail to account for the strong correlation present from one measurement to another, potentially leading to erroneous findings of significance such as those demonstrated in this analysis.

LELI research must be accompanied by the use of rigorous statistical analysis in order to support claims of laser efficacy. Repeated measures linear regression analysis techniques offer a powerful tool to ensure that suitable statistical rigor is applied to the analysis of LELI experimental data so that reported results will be believable and reproducible. Failure to progress on this front will continue to hamper the advancement of LELI research.

ACKNOWLEDGMENTS

Special thanks to Dr. Rob Leighty, Dr. Susan Volman, Dr. Bradley Clymer, and Ms. Peiling Yang for their advice and assistance.

This work was funded by the American Society for Laser Medicine and Surgery (ASLMS) as part of the Graduate Student Summer Research Grant Program. D.W.E. is currently a Whitaker Foundation Doctoral Fellow in Biomedical Engineering at Ohio State University.

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